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Linezolid and Glucose Injection Package Insert

Please read the package insert carefully and use under the direction of the Physician

[Drug names]

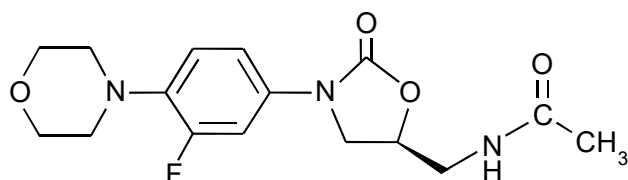
Chinese Generic Name: Linezolid and Glucose Injection
Old Generic Name: Linezolid Injection
Chinese Trade Name: Si Wo®\Zyvox®
English Generic Name: Linezolid and Glucose Injection
Chinese Pinyin: Linaizuoan Putaotang Zhusheyeye

[Ingredients]

Active ingredients as well as their chemical names:

Linezolid;(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide.

Structural formula:



Molecular formula: C₁₆H₂₀FN₃O₄

Molecular weight: 337.35

Inactive ingredients are sodium citrate, citric acid, and dextrose in an aqueous vehicle for intravenous administration. The sodium (Na⁺) content is 0.38 mg/mL (5 mEq per 300-mL bag).

[Description]

This product is colorless to light brown liquid.

[Indications]

ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and

-resistant strains), or *Streptococcus pneumoniae*.

Community-acquired pneumonia caused by *Streptococcus pneumoniae*, including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*.

Vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

Linezolid is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see **Warnings**).

[Strength]

300 mL: linezolid 600 mg and glucose 13.7 g.

[Dosage and administration]

The recommended dosage for ZYVOX formulations for the treatment of infections is described in Table 1.

Table 1. Dosage Guidelines for ZYVOX

Infection *	Dosage, Route and Frequency of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients† (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Nosocomial pneumonia Community-acquired pneumonia, including concurrent bacteremia Complicated skin and skin structure infections	10 mg/kg IV or oral† q8h	600 mg IV or oral† q12h	10 to 14
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg IV or oral† q8h	600 mg IV or oral† q12h	14 to 28
Uncomplicated skin and skin structure infections	less than 5 yrs: 10 mg/kg oral† q8h 5-11 yrs: 10 mg/kg oral q12h†	Adults: 400 mg oral† q12h Adolescents: 600 mg oral q12h†	10 to 14

* Due to the designated pathogens (see [Indications]).

† **Neonates less than 7 days:** Most pre-term neonates less than 7 days of age (gestational age less than 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life (see [Pharmacokinetics], **Special populations – Pediatric**).

† Oral dosing using either ZYVOX Tablets or ZYVOX for Oral Suspension.

Adult patients with infection due to MRSA should be treated with ZYVOX 600 mg q12h.

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see [Pharmacokinetics], **Special populations, Pediatric** and [Precautions], [Pediatric use]).

In controlled clinical trials, the protocol-defined duration of treatment for all infections ranged from 7 to 28 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response.

No dose adjustment is necessary when switching from intravenous to oral administration. Patients whose therapy is started with ZYVOX I.V. Injection may be switched to either ZYVOX Tablets or Oral Suspension at the discretion of the physician, when clinically indicated.

Intravenous administration

ZYVOX I.V. Injection is supplied in single-use, ready-to-use infusion bags. Parenteral drug products should be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bag. If leaks are detected, discard the solution, as sterility may be impaired.

ZYVOX I.V. Injection should be administered by intravenous infusion over a period of 30 to 120 minutes. **Do not use this intravenous infusion bag in series connections.** Additives should not be introduced into this solution. If ZYVOX I.V. Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product. In particular, physical incompatibilities resulted when ZYVOX I.V. Injection was combined with the following drugs during simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium, and trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when ZYVOX I.V. Injection was combined with ceftriaxone sodium.

If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of ZYVOX I.V. Injection with an infusion solution compatible with ZYVOX I.V. Injection and with any other drug(s) administered via this common line (see **Compatible intravenous solutions**).

Compatible intravenous solutions

5% Dextrose Injection, USP

0.9% Sodium Chloride Injection, USP

Lactated Ringer's Injection, USP

Keep the infusion bags in the overwrap until ready to use. Store at room temperature. Protect from freezing. ZYVOX I.V. Injection may exhibit a yellow color that can intensify over time without adversely affecting potency.

[Adverse reactions]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult patients

The safety of ZYVOX formulations was evaluated in 2,046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days.

Of the patients treated for uncomplicated skin and skin structure infections (uSSSIs), 25.4% of ZYVOX-treated and 19.6% of comparator-treated patients experienced at least one drug-related adverse event. For all other indications, 20.4% of ZYVOX -treated and 14.3% of comparator-treated patients experienced at least one drug-related adverse event.

In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. Table 2 shows the incidence of adverse events reported in at least 2% of patients in these trials. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%).

Table 2 Incidence (%) of Adverse Events Reported in \geq 2% of Adult Patients in Comparator-controlled Clinical Trials with ZYVOX

Event	ZYVOX (n=2046)	All Comparators * (n=2001)
Diarrhea	8.3	6.3
Headache	6.5	5.5
Nausea	6.2	4.6
Vomiting	3.7	2.0
Insomnia	2.5	1.7
Constipation	2.2	2.1
Rash	2.0	2.2
Dizziness	2.0	1.9
Fever	1.6	2.1

* Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration.

Table 3 shows the incidence of all-causality, treatment-emergent adverse events reported in at least 1% of adult patients in these trials by dose of ZYVOX.

Table 3. Incidence (%) of Treatment-emergent Adverse Reactions Occurring in >1% of Adult Patients Treated with ZYVOX in Comparator-controlled Clinical Trials

<u>ADVERSE REACTIONS</u>	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg by mouth every 12 hours (n=548)	Clarithromycin 250 mg by mouth every 12 hours (n=537)	ZYVOX 600 mg every 12 hours (n=1498)	All Other Comparators* (n=1464)
Headache	8.8	8.4	5.7	4.4
Diarrhea	8.2	6.1	8.3	6.4
Nausea	5.1	4.5	6.6	4.6
Vomiting	2.0	1.5	4.3	2.3
Dizziness	2.6	3.0	1.8	1.5
Rash	1.1	1.1	2.3	2.6
Anemia	0.4	0	2.1	1.4
Taste alteration	1.8	2.0	1.0	0.3
Vaginal moniliasis	1.8	1.3	1.1	0.5
Oral moniliasis	0.5	0	1.7	1.0
Abnormal liver function tests	0.4	0.2	1.6	0.8
Fungal infection	1.5	0.2	0.3	0.2
Tongue discoloration	1.3	0	0.3	0
Localized abdominal pain	1.3	0.6	1.2	0.8
Generalized abdominal pain	0.9	0.4	1.2	1.0

* Comparators included cefpodoxime proxetil 200 mg by mouth every 12 hours; ceftriaxone 1 g intravenously every 12 hours; dicloxacillin 500 mg by mouth every 6 hours; oxacillin 2 g intravenously every 6 hours; vancomycin 1 g intravenously every 12 hours.

Of the patients treated for uSSSIs, 3.5% of ZYVOX-treated and 2.4% of comparator-treated patients discontinued treatment due to drug-related adverse events. For all other indications, discontinuations due to drug-related adverse events occurred in 2.1% of ZYVOX -treated and 1.7% of comparator-treated patients. The most common reported drug-related adverse events leading to discontinuation of treatment were nausea, headache, diarrhea, and vomiting.

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 2,000 adult patients who received the recommended linezolid doses for up to 28 days. Those most commonly reported were diarrhoea (8.4%), headache (6.5%), nausea (6.3%) and vomiting (4.0%).

The most commonly reported drug-related adverse events which led to discontinuation of treatment were headache, diarrhoea, nausea and vomiting. About 3% of patients discontinued treatment because they experienced a drug-related adverse event.

Additional adverse reactions reported from post-marketing experience are included in the table with frequency category 'Not known', since the actual frequency cannot be estimated from the available data.

The following undesirable effects have been observed and reported during treatment with linezolid with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); Not known (cannot be estimated from the available data)

System Organ Class	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1\ 000$ to $< 1/100$)	Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$)	Very Rare ($< 1/10\ 000$)	Frequency not known (cannot be estimated from available data)
Infections and infestations	Candidiasis, oral candidiasis, vaginal candidiasis, fungal infections	vaginitis	antibiotic-associated colitis, incl. pseudomembranous colitis*		
Blood and the lymphatic system disorders	anaemia*†	leucopenia*, neutropenia, thrombocytopenia*, eosinophilia	pancytopenia*		Myelosuppression*, sideroblastic
Immune system disorders					anaphylaxis
Metabolism and nutrition disorders		hyponatraemia			Lactic acidosis*
Psychiatric disorders	Insomnia				

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Very Rare (<1/10 000)	Frequency not known (cannot be estimated from available data)
Nervous system disorders	headache, taste perversion (metallic taste), dizziness	convulsions*, hypoaesthesia, paraesthesia			serotonin syndrome**, peripheral neuropathy*
Eye disorders		blurred vision*	changes in visual field defect*		Optic neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*
Ear and labyrinth disorders		tinnitus			
Cardiac disorders		Arrhythmia (tachycardia)			
Vascular disorders	hypertension	Transient ischaemic attacks, phlebitis, thrombophlebitis			
Gastrointestinal disorders	diarrhoea, nausea, vomiting, localised or general abdominal pain, constipation, dyspepsia.	pancreatitis, gastritis, abdominal distension dry mouth, glossitis, loose stools, stomatitis, tongue discoloration or disorder	Superficial tooth discoloration		
Hepato-biliary disorders	abnormal liver function test; increased AST, ALT or alkaline phosphatase	increased total bilirubin			

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Very Rare (<1/10 000)	Frequency not known (cannot be estimated from available data)
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria, dermatitis, diaphoresis			bullous disorders such as those described as Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, alopecia
Renal and urinary disorders	increased BUN	Renal failure, increased creatinine, polyuria			
Reproductive system and breast disorders		vulvovaginal disorder			
General disorders and administration site conditions	fever, localised pain	chills, fatigue, injection site pain, increased thirst			

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Very Rare (<1/10 000)	Frequency not known (cannot be estimated from available data)
Investigations	<u>Chemistry</u> Increased LDH, creatine kinase, lipase, amylase or non-fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate. <u>Haematology</u> increased neutrophils or eosinophils. decreased haemoglobin, haematocrit or red blood cell count. decreased or increased platelet or white blood cell counts.	<u>Chemistry</u> Increased sodium or calcium. Decreased non-fasting glucose. Increased or decreased chloride. <u>Haematology</u> Increased reticulocyte count, decreased neutrophils.			

* See [Precautions].

** See [Contraindications] and [Precautions].

† See below.

The following adverse reactions to linezolid were considered to be serious in rare cases: localised abdominal pain, transient ischaemic attacks and hypertension.

In controlled clinical trials where linezolid was administered for up to 28 days, anaemia was reported in 2% of the patients. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who

developed anaemia when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for > 28 days. The proportion of cases reporting drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for > 28 days.

Pediatric patients

Safety data from clinical studies based on around 500 paediatric patients (from birth to 17 years) do not indicate that the safety profile of linezolid for paediatric patients differs from that for adult patients.

The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid: vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. Table 4 shows the incidence of adverse events reported in at least 2% of pediatric patients treated with ZYVOX in these trials.

Of the pediatric patients treated for uSSSIs, 19.2% of ZYVOX-treated and 14.1% of comparator-treated patients experienced at least one drug-related adverse event. For all other indications, 18.8% of ZYVOX-treated and 34.3% of comparator-treated patients experienced at least one drug-related adverse event.

Table 4. Incidence (%) of Adverse Events Reported in $\geq 2\%$ of Pediatric Patients Treated with ZYVOX in Comparator-controlled Clinical Trials

Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications**	
	ZYVOX (n=248)	Cefadroxil (n = 251)	ZYVOX (n = 215)	Vancomycin (n=101)
Fever	2.9	3.6	14.1	14.1
Diarrhea	7.8	8.0	10.8	12.1
Vomiting	2.9	6.4	9.4	9.1
Sepsis	0	0	8.0	7.1
Rash	1.6	1.2	7.0	15.2
Headache	6.5	4.0	0.9	0
Anemia	0	0	5.6	7.1
Thrombocytopenia	0	0	4.7	2.0
Upper respiratory infection	3.7	5.2	4.2	1.0
Nausea	3.7	3.2	1.9	0

Dyspnea	0	0	3.3	1.0
Reaction at site of injection or of vascular catheter	0	0	3.3	5.1
Trauma	3.3	4.8	2.8	2.0
Pharyngitis	2.9	1.6	0.5	1.0
Convulsion	0	0	2.8	2.0
Hypokalemia	0	0	2.8	3.0
Pneumonia	0	0	2.8	2.0
Thrombocythemia	0	0	2.8	2.0
Cough	2.4	4.0	0.9	0
Generalized abdominal pain	2.4	2.8	0.9	2.0
Localized abdominal pain	2.4	2.8	0.5	1.0
Apnea	0	0	2.3	2.0
Gastrointestinal bleeding	0	0	2.3	1.0
Generalized edema	0	0	2.3	1.0
Loose stools	1.6	0.8	2.3	3.0
Localized pain	2.0	1.6	0.9	0
Skin disorder	2.0	0	0.9	1.0

* Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

** Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Table 5 shows the incidence of all-causality, treatment-emergent adverse events reported in more than 1% of pediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

Table 5. Incidence (%) of Treatment-emergent Adverse Reactions Occurring in >1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-controlled Clinical Trials

ADVERSE REACTIONS	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
	ZYVOX (n=248)	Cefadroxil (n=251)	ZYVOX (n=215)	Vancomycin (n=101)
Diarrhea	7.8	8.0	10.8	12.1
Vomiting	2.9	6.4	9.4	9.1
Headache	6.5	4.0	0.9	0
Anemia	0	0	5.6	7.1
Thrombocytopenia	0	0	4.7	2.0
Nausea	3.7	3.2	1.9	0
Generalized abdominal pain	2.4	2.8	0.9	2.0
Localized abdominal pain	2.4	2.8	0.5	1.0
Loose stools	1.6	0.8	2.3	3.0
Eosinophilia	0.4	0.8	1.9	1.0
Pruritus at non-application site	0.8	0.4	1.4	2.0
Vertigo	1.2	0.4	0	0

* Patients 5 through 11 years of age received ZYVOX 10 mg/kg by mouth every 12 hours or cefadroxil 15 mg/kg by mouth every 12 hours. Patients 12 years or older received ZYVOX 600 mg by mouth every 12 hours or cefadroxil 500 mg by mouth every 12 hours.

† Patients from birth through 11 years of age received ZYVOX 10 mg/kg intravenously by mouth every 8 hours or vancomycin 10 to 15 mg/kg intravenously every 6-24 hours, depending on age and renal clearance.

Of the pediatric patients treated for uSSSIs, 1.6% of ZYVOX-treated and 2.4% of comparator-treated patients discontinued treatment due to drug-related adverse events. For all other indications, discontinuations due to drug-related adverse events occurred in 0.9% of ZYVOX-treated and 6.1% of comparator-treated patients.

Laboratory changes

ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The

platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **Warnings**).

Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The incidence of adult and pediatric patients with at least one substantially abnormal hematologic or serum chemistry value is presented in Tables 6, 7, 8, and 9.

Table 6. Percent of Adult Patients who Experienced at Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg q12h	Clarithromycin 250 mg q12h	ZYVOX 600 mg q12h	All Other Comparators**
Hemoglobin (g/dL)	0.9	0.0	7.1	6.6
Platelet count (x 10 ³ /mm ³)	0.7	0.8	3.0	1.8
WBC (x 10 ³ /mm ³)	0.2	0.6	2.2	1.3
Neutrophils (x 10 ³ /mm ³)	0.0	0.2	1.1	1.2

* <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

** Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Table 7. Percent of Adult Patients who Experienced at Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg q12h	Clarithromycin 250 mg q12h	ZYVOX 600 mg q12h	All Other Comparators**
AST (U/L)	1.7	1.3	5.0	6.8
ALT (U/L)	1.7	1.7	9.6	9.3
LDH (U/L)	0.2	0.2	1.8	1.5
Alkaline phosphatase (U/L)	0.2	0.2	3.5	3.1
Lipase (U/L)	2.8	2.6	4.3	4.2
Amylase (U/L)	0.2	0.2	2.4	2.0
Total bilirubin (mg/dL)	0.2	0.0	0.9	1.1
BUN (mg/dL)	0.2	0.0	2.1	1.5
Creatinine (mg/dL)	0.2	0.0	0.2	0.6

- * >2 x Upper Limit of Normal (ULN) for values normal at baseline;
 >2 x ULN and >2 x baseline for values abnormal at baseline.
- ** Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Table 8. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections**		All Other Indications***	
	ZYVOX	Cefadroxil	ZYVOX	Vancomycin
Hemoglobin (g/dL)	0.0	0.0	15.7	12.4
Platelet count (x 10 ³ /mm ³)	0.0	0.4	12.9	13.4
WBC (x 10 ³ /mm ³)	0.8	0.8	12.4	10.3
Neutrophils (x 10 ³ /mm ³)	1.2	0.8	5.9	4.3

- * <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.
- ** Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.
- *** Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Table 9. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections**		All Other Indications***	
	ZYVOX	Cefadroxil	ZYVOX	Vancomycin
ALT (U/L)	0.0	0.0	10.1	12.5
Lipase (U/L)	0.4	1.2	---	---
Amylase (U/L)	---	---	0.6	1.3
Total bilirubin (mg/dL)	---	---	6.3	5.2
Creatinine (mg/dL)	0.4	0.0	2.4	1.0

- * >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.
- ** Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.
- *** Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Post-marketing experience

- Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) (see **Warnings**); sideroblastic anemia.

- Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision.
- Lactic acidosis (see **[Precautions], General**). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy.
- Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **[Precautions], General**).
- Convulsions (see **[Precautions], General**).
- Anaphylaxis, angioedema, and bullous skin disorders including severe cutaneous adverse reactions (SCAR) such as toxic epidermal necrolysis and Stevens Johnson syndrome.
- Superficial tooth discoloration and tongue discoloration have been reported with the use of linezolid. The tooth discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome.
- Hypoglycemia, including symptomatic episodes (see **Warnings**).

These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established.

[Contraindications]

ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

Monoamine oxidase inhibitors

Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within two weeks of taking any such medicinal product.

Potential interactions producing elevation of blood pressure

Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant medications:

- Patients with uncontrolled hypertension, pheochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.

- Patients taking any of the following types of medications: serotonin re-uptake inhibitors (see **[Precautions]**), tricyclic antidepressants, serotonin 5-HT₁ receptor agonists (triptans), directly and indirectly acting sympathomimetic agents (e.g. the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone (see **[Precautions]**, **Drug interactions**).

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breast-feeding should be discontinued prior to and throughout administration (see **[Pregnancy and lactation]**).

Potential serotonergic interactions

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT₁ receptor agonists (triptans), meperidine or buspirone (see **[Precautions]**, **General and Drug interactions**).

[Precautions]

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX formulations and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Warnings

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pre-treatment levels. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with linezolid may be at greater risk of experiencing blood dyscrasias than younger patients. Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis.

Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing anaemia, granulocytopenia or thrombocytopenia, myelosuppression, those receiving concomitant drugs that decrease haemoglobin levels, depress white blood cell counts, adversely affect platelet count or function, produce bone marrow suppression, have severe renal insufficiency; receive more than 10-14 days of therapy or those with a chronic infection who have received previous or concomitant antibiotic therapy. Linezolid should be administered to such patients only when close monitoring of haemoglobin levels, white blood cell counts and platelet counts is possible.

Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression, unless it is considered absolutely necessary to

continue therapy, in which case intensive monitoring of blood counts and appropriate management strategies should be implemented.

In addition, it is recommended that complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) should be monitored weekly in patients who receive linezolid regardless of baseline blood count.

In compassionate use studies, a higher incidence of serious anaemia was reported in patients receiving linezolid for more than the maximum recommended duration of 28 days. These patients more often required blood transfusion. Cases of anaemia requiring blood transfusion have also been reported post-marketing, with more cases occurring in patients who received linezolid therapy for more than 28 days.

Cases of sideroblastic anaemia have been reported post-marketing. Where time of onset was known, most patients had received linezolid therapy for more than 28 days. Most patients fully or partially recovered following discontinuation of linezolid with or without treatment for their anaemia.

In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed (see [Pharmacology and Toxicology]).

Mortality Imbalance in an Investigational Study in Patients with Catheter-related Bloodstream Infections, including those with catheter-site infections.

An imbalance in mortality was seen in patients treated with linezolid relative to vancomycin/dicloxacillin/oxacillin in an open-label study in seriously ill patients with intravascular catheter-related infections [78/363 (21.5%) vs. 58/363 (16.0%); odds ratio 1.426, 95% CI 0.970, 2.098]. While causality has not been established, this observed imbalance occurred primarily in linezolid-treated patients in whom either Gram-negative pathogens, mixed Gram-negative and Gram-positive pathogens, or no pathogen were identified at baseline, but was not seen in patients with Gram-positive infections only. The main factor influencing the mortality rate was the Gram positive infection status at baseline. Mortality rates were similar in patients with infections caused purely by Gram positive organisms (odds ratio 0.96; 95% confidence interval: 0.58-1.59) but were significantly higher ($p=0.0162$) in the linezolid arm in patients with any other pathogen or no pathogen at baseline (odds ratio 2.48; 95% confidence interval: 1.38-4.46). The greatest imbalance occurred during treatment and within 7 days following discontinuation of study drug. More patients in the linezolid arm acquired Gram negative pathogens during the study and died from infection caused by Gram negative pathogens and polymicrobial infections. Therefore, in complicated skin and soft tissue infections linezolid should only be used in patients with known or possible co-infection with Gram negative organisms if there are no alternative treatment options available. In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

Linezolid is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

Linezolid has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see [Indications] and [Dosage and administration]).

Antibiotic-associated diarrhoea and colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent. In cases of suspected or verified antibiotic-associated colitis, discontinuation of linezolid may be warranted. Appropriate management measures should be instituted.

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of linezolid. If CDAD is suspected or confirmed, ongoing treatment with antibiotic agents, including linezolid, not directed against *C. difficile*, should be discontinued and adequate therapeutic measures should be initiated immediately. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. Drugs inhibiting peristalsis are contraindicated in this situation.

Hypoglycemia

Post-marketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid, a reversible, non-selective MAO inhibitor. Some MAO inhibitors have been associated with hypoglycemic episodes in diabetic patients receiving insulin or hypoglycemic agents. While a causal relationship between linezolid and hypoglycemia has not been established, diabetic

patients should be cautioned of potential hypoglycemic reactions when treated with linezolid. If hypoglycemia occurs, a decrease in the dose of insulin or oral hypoglycemic agent, or discontinuation of oral hypoglycemic agent, insulin, or linezolid may be required.

General

Lactic acidosis

Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, abdominal pain, unexplained acidosis, a low bicarbonate level, or hyperventilation while receiving ZYVOX should receive immediate medical evaluation. If lactic acidosis occurs, the benefits of continued use of linezolid should be weighed against the potential risks.

Mitochondrial dysfunction

Linezolid inhibits mitochondrial protein synthesis. Adverse events, such as lactic acidosis, anaemia and neuropathy (optic and peripheral), may occur as a result of this inhibition; these events are more common when the drug is used longer than 28 days.

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see [Precautions], Drug interactions). Co-administration of linezolid and serotonergic agents is therefore contraindicated (see [Contraindications]).

Unless clinically appropriate and patients are carefully observed for signs and/or symptoms of serotonin syndrome or neuroleptic malignant syndrome-like (NMS-like) reactions, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT₁ receptor agonists (triptans), meperidine, bupropion, or buspirone.

Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents.

In some cases, a patient already receiving a serotonergic antidepressant or buspirone may require urgent treatment with linezolid. If alternatives to linezolid are not available and the potential benefits of linezolid outweigh the risks of serotonin syndrome or NMS-like reactions, the serotonergic antidepressant should be stopped promptly and linezolid administered. The patient should be monitored for two weeks (five weeks if fluoxetine was taken) or until 24 hours after the last dose of linezolid, whichever comes

first. Symptoms of serotonin syndrome or NMS-like reactions include hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that include extreme agitation progressing to delirium and coma. The patient should also be monitored for discontinuation symptoms of the antidepressant.

If signs or symptoms occur physicians should consider discontinuing either one or both agents; If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).

Peripheral and optic neuropathy

Peripheral, optic neuropathy, and optic neuritis have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days.

If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks.

There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medications for the treatment of tuberculosis.

Convulsions

Convulsions have been reported in patients when treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported. Patients should be advised to inform their physician if they have a history of seizures.

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI); however, at the doses used for antibacterial therapy, it does not exert an anti-depressive effect. There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible.

Superinfection

The effects of linezolid therapy on normal flora have not been evaluated in clinical trials. The use of antibiotics may promote the overgrowth of non-susceptible organisms. For example,

approximately 3% of patients receiving the recommended linezolid doses experienced drug-related candidiasis during clinical trials. Should superinfection occur during therapy, appropriate measures should be taken.

Special populations

Linezolid should be used in patients with severe renal insufficiency only when the anticipated benefit is considered to outweigh the theoretical risk, and close monitor on patient is required.

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk.

ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

Clinical trials

The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

Development of Drug-resistant Bacteria

Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Use with tyramine-rich foods

Patients should be advised against consuming large amounts of tyramine rich foods.

Information for patients

Patients should be advised that:

- ZYVOX may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

- They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants.
- They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants.
- *Phenylketonurics*: Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist.
- They should inform their physician if they experience changes in vision.
- They should inform their physician if they have a history of seizures.
- Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g. the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future.

Drug interactions (see also [Pharmacology and toxicology], [Interactions of drugs])

Monoamine oxidase inhibition: Linezolid is a reversible, non-selective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic agents: Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response.

Serotonergic agents: Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the Precautions, General section.

Strong CYP450 Inducers: In a study in healthy volunteers, co-administration of rifampin with oral linezolid resulted in a 21% decrease in linezolid C_{max} and a 32% decrease in linezolid

AUC₀₋₁₂. The clinical significance of this interaction is unknown. Other strong inducers of hepatic enzymes (e.g. carbamazepine, phenytoin, phenobarbital) could cause a similar or smaller decrease in linezolid exposure (see [Pharmacology and toxicology], [Interactions of drugs]).

Drug-laboratory test interactions

There are no reported drug-laboratory test interactions.

[Pregnancy and lactation]

Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman.

There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

[Pediatric use]

The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see [Indications] and [Clinical studies]):

- nosocomial pneumonia
- complicated skin and skin structure infections
- community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years)
- vancomycin-resistant *Enterococcus faecium* infections

The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years (see [Clinical studies]):

- uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*

Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended.

The pharmacokinetics of linezolid have been evaluated in pediatric patients from birth to 17 years of age. In general, weight-based clearance of linezolid gradually decreases with increasing age of pediatric patients. However, in preterm (gestational age <34 weeks) neonates <7 days of age, linezolid clearance is often lower than in full-term neonates <7 days of age. Consequently, preterm neonates <7 days of age may need an alternative linezolid dosing regimen of 10 mg/kg every 12 hours (see **[Pharmacokinetics], Special populations, Pediatric and [Dosage and administration]**).

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 mcg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 mcg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see **[Pharmacokinetics], Special populations, Pediatric and [Dosage and administration]**).

[Geriatric use]

Of the 2,046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

[Interactions of drugs]

Drugs metabolized by cytochrome P450: Linezolid is not an inducer of cytochrome P450 (CYP450) in rats. In addition, linezolid does not inhibit the activities of clinically significant human CYP isoforms (e.g. 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, linezolid is not expected to affect the pharmacokinetics of other drugs metabolized by these major enzymes. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Antibiotics

Aztreonam: The pharmacokinetics of linezolid or aztreonam are not altered when administered together.

Gentamicin: The pharmacokinetics of linezolid or gentamicin are not altered when administered together.

Antioxidants

The potential for drug-drug interactions with linezolid and the antioxidants Vitamin C and Vitamin E was studied in healthy volunteers. Subjects were administered a 600 mg oral dose of linezolid on Day 1, and another 600 mg dose of linezolid on Day 8. On Days 2-9, subjects were given either Vitamin C (1000 mg/day) or Vitamin E (800 IU/day). The $AUC_{0-\infty}$ of linezolid increased 2.3% when co-administered with Vitamin C and 10.9% when co-administered with Vitamin E. No linezolid dose adjustment is recommended during co-administration with Vitamin C or Vitamin E.

Strong CYP 3A4 Inducers

Rifampin: The effect of rifampin on the pharmacokinetics of linezolid was evaluated in a study of 16 healthy adult males. Volunteers were administered oral linezolid 600 mg twice daily for 5 doses with and without rifampin 600 mg once daily for 8 days. Co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid C_{max} [90% CI, 15%-27%] and a 32% decrease in linezolid AUC_{0-12} [90% CI, 27%-37%]. The clinical significance of this interaction is unknown. The mechanism of this interaction is not fully understood and may be related to the induction of hepatic enzymes. Other strong inducers of hepatic enzymes (e.g. carbamazepine, phenytoin, phenobarbital) could cause a similar or smaller decrease in linezolid exposure.

Monoamine oxidase inhibition

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic agents

Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response.

Tyramine: A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content.

Pseudoephedrine HCl or phenylpropanolamine HCl: A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects (see **[Precautions]**, **Drug interactions**). A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg q12h for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments. Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2 to

3 hours after the second dose of PPA or PSE, and returned to baseline 2 to 3 hours after peak. The results of the PPA study follow, showing the mean (and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg (range: 20-52 mm Hg) and 38 mm Hg (range: 18-79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively.

Serotonergic agents

Dextromethorphan: The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20-mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

[Overdose]

In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

[Clinical studies]

Adults

Nosocomial pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a randomized, multi-center, double-blind trial. Patients were treated for 7 to 21 days. One group received ZYVOX I.V. Injection 600 mg q12h, and the other group received vancomycin 1 g q12h IV. Both groups received concomitant aztreonam (1 to 2 g every 8 hours IV), which could be continued if clinically indicated. There were 203 linezolid-treated and 193 vancomycin-treated patients enrolled in the study. One hundred twenty-two (60%) linezolid-treated patients and 103 (53%) vancomycin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 57% for linezolid-treated patients and 60% for vancomycin-treated patients. The cure rates in clinically evaluable patients with ventilator-associated pneumonia were 47% for linezolid-treated patients and 40% for vancomycin-treated patients. A modified intent-to-treat (MITT) analysis of 94 linezolid-treated patients and 83 vancomycin-treated patients included subjects who had a pathogen isolated before treatment. The cure rates in the MITT analysis were 57% in linezolid-treated patients and 46% in vancomycin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 10

Table 10. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Nosocomial Pneumonia

Pathogen	Cured	
	ZYVOX n/N (%)	Vancomycin n/N (%)
<i>Staphylococcus aureus</i>	23/38 (61)	14/23 (61)
Methicillin-resistant <i>S. aureus</i>	13/22 (59)	7/10 (70)
<i>Streptococcus pneumoniae</i>	9/9 (100)	9/10 (90)

Complicated skin and skin structure infections

Adult patients with clinically documented complicated skin and skin structure infections were enrolled in a randomized, multi-center, double-blind, double-dummy trial comparing study medications administered IV followed by medications given orally for a total of 10 to 21 days of treatment. One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX Tablets 600 mg q12h; the other group received oxacillin 2 g every 6 hours (q6h) IV followed by dicloxacillin 500 mg q6h orally. Patients could receive concomitant aztreonam if clinically indicated. There were 400 linezolid-treated and 419 oxacillin-treated patients enrolled in the study. Two hundred forty-five (61%) linezolid-treated patients and 242 (58%) oxacillin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 90% in linezolid-treated patients and 85% in oxacillin-treated patients. A modified intent-to-treat (MITT) analysis of 316 linezolid-treated patients and 313 oxacillin-treated patients included subjects who met all criteria for study entry. The cure rates in the MITT analysis were 86% in linezolid-treated patients and 82% in oxacillin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 11.

Table 11. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Complicated Skin and Skin Structure Infections

Pathogen	Cured	
	ZYVOX n/N (%)	Oxacillin/Dicloxacillin n/N (%)
<i>Staphylococcus aureus</i>	73/83 (88)	72/84 (86)
Methicillin-resistant <i>S. aureus</i>	2/3 (67)	0/0 (-)
<i>Streptococcus agalactiae</i>	6/6 (100)	3/6 (50)
<i>Streptococcus pyogenes</i>	18/26 (69)	21/28 (75)

A separate study provided additional experience with the use of ZYVOX in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. This was a randomized, open-label trial in hospitalized adult patients with documented or suspected MRSA infection.

One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX Tablets 600 mg q12h. The other group of patients received vancomycin 1 g q12h IV. Both groups were treated for 7 to 28 days, and could receive concomitant aztreonam or gentamicin

if clinically indicated. The cure rates in microbiologically evaluable patients with MRSA skin and skin structure infection were 26/33 (79%) for linezolid-treated patients and 24/33 (73%) for vancomycin-treated patients.

Diabetic foot infections

Adult diabetic patients with clinically documented complicated skin and skin structure infections (“diabetic foot infections”) were enrolled in a randomized (2:1 ratio), multi-center, open-label trial comparing study medications administered IV or orally for a total of 14 to 28 days of treatment. One group of patients received ZYVOX 600 mg q12h IV or orally; the other group received ampicillin/sulbactam 1.5 to 3 g IV or amoxicillin/clavulanate 500 to 875 mg every 8 to 12 hours (q8-12h) orally. In countries where ampicillin/sulbactam is not marketed, amoxicillin/clavulanate 500 mg to 2 g every 6 hours (q6h) was used for the intravenous regimen. Patients in the comparator group could also be treated with vancomycin 1 g q12h IV if MRSA was isolated from the foot infection. Patients in either treatment group who had Gram-negative bacilli isolated from the infection site could also receive aztreonam 1 to 2 g q8-12h IV. All patients were eligible to receive appropriate adjunctive treatment methods, such as debridement and off-loading, as typically required in the treatment of diabetic foot infections, and most patients received these treatments. There were 241 linezolid-treated and 120 comparator-treated patients in the intent-to-treat (ITT) study population. Two hundred twelve (86%) linezolid-treated patients and 105 (85%) comparator-treated patients were clinically evaluable. In the ITT population, the cure rates were 68.5% (165/241) in linezolid-treated patients and 64% (77/120) in comparator-treated patients, where those with indeterminate and missing outcomes were considered failures. The cure rates in the clinically evaluable patients (excluding those with indeterminate and missing outcomes) were 83% (159/192) and 73% (74/101) in the linezolid- and comparator-treated patients, respectively. A critical post-hoc analysis focused on 121 linezolid-treated and 60 comparator-treated patients who had a Gram-positive pathogen isolated from the site of infection or from blood, who had less evidence of underlying osteomyelitis than the overall study population, and who did not receive prohibited antimicrobials. Based upon that analysis, the cure rates were 71% (86/121) in the linezolid-treated patients and 63% (38/60) in the comparator-treated patients. None of the above analyses were adjusted for the use of adjunctive therapies. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 12.

Table 12. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Diabetic Foot Infections

Pathogen	Cured	
	ZYVOX n/N (%)	Comparator n/N (%)
<i>Staphylococcus aureus</i>	49/63 (78)	20/29 (69)
Methicillin-resistant <i>S. aureus</i>	12/17 (71)	2/3 (67)
<i>Streptococcus agalactiae</i>	25/29 (86)	9/16 (56)

Vancomycin-resistant enterococcal infections

Adult patients with documented or suspected vancomycin-resistant enterococcal infection were enrolled in a randomized, multi-center, double-blind trial comparing a high dose of ZYVOX (600 mg) with a low dose of ZYVOX (200 mg) given every 12 hours (q12h) either intravenously (IV) or orally for 7 to 28 days. Patients could receive concomitant aztreonam or aminoglycosides. There were 79 patients randomized to high-dose linezolid and 66 to low-dose linezolid. The intent-to-treat (ITT) population with documented vancomycin-resistant enterococcal infection at baseline consisted of 65 patients in the high-dose arm and 52 in the low-dose arm.

The cure rates for the ITT population with documented vancomycin-resistant enterococcal infection at baseline are presented in Table 13 by source of infection. These cure rates do not include patients with missing or indeterminate outcomes. The cure rate was higher in the high-dose arm than in the low-dose arm, although the difference was not statistically significant at the 0.05 level.

Table 13. Cure Rates at the Test-of-Cure Visit for ITT Adult Patients with Documented Vancomycin-resistant Enterococcal Infections at Baseline

Source of Infection	Cured	
	ZYVOX 600 mg q12h n/N (%)	ZYVOX 200 mg q12h n/N (%)
Any site	39/58 (67)	24/46 (52)
Any site with associated bacteremia	10/17 (59)	4/14 (29)
Bacteremia of unknown origin	5/10 (50)	2/7 (29)
Skin and skin structure	9/13 (69)	5/5 (100)
Urinary tract	12/19 (63)	12/20 (60)
Pneumonia	2/3 (67)	0/1 (0)
Other*	11/13 (85)	5/13 (39)

* Includes sources of infection such as hepatic abscess, biliary sepsis, necrotic gall bladder, pericolic abscess, pancreatitis, and catheter-related infection.

Pediatric patients

Infections due to Gram-positive organisms

A safety and efficacy study provided experience on the use of ZYVOX in pediatric patients for the treatment of nosocomial pneumonia, complicated skin and skin structure infections, and other infections due to Gram-positive bacterial pathogens, including methicillin-resistant and -susceptible *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Pediatric patients ranging in age from birth through 11 years with infections caused by the documented or suspected Gram-positive organisms were enrolled in a randomized, open-label, comparator-controlled trial. One group of patients received ZYVOX I.V. Injection 10 mg/kg every 8 hours (q8h) followed by ZYVOX for Oral Suspension 10 mg/kg q8h. A second group received vancomycin 10 to 15 mg/kg IV every 6 to 24 hours, depending on age

and renal clearance. Patients who had confirmed VRE infections were placed in a third arm of the study and received ZYVOX 10 mg/kg q8h IV and/or orally. All patients were treated for a total of 10 to 28 days and could receive concomitant Gram-negative antibiotics if clinically indicated. In the intent-to-treat (ITT) population, there were 206 patients randomized to linezolid and 102 patients randomized to vancomycin. One hundred seventeen (57%) linezolid-treated patients and 55 (54%) vancomycin-treated patients were clinically evaluable. The cure rates in ITT patients were 81% in patients randomized to linezolid and 83% in patients randomized to vancomycin (95% Confidence Interval of the treatment difference; -13%, 8%). The cure rates in clinically evaluable patients were 91% in linezolid-treated patients and 91% in vancomycin-treated patients (95% CI; -11%, 11%). Modified intent-to-treat (MITT) patients included ITT patients who, at baseline, had a Gram-positive pathogen isolated from the site of infection or from blood. The cure rates in MITT patients were 80% in patients randomized to linezolid and 90% in patients randomized to vancomycin (95% CI; -23%, 3%). The cure rates for ITT, MITT, and clinically evaluable patients are presented in Table 14.

After the study was completed, 13 additional patients ranging from 4 days through 16 years of age were enrolled in an open-label extension of the VRE arm of the study. Table 15 provides clinical cure rates by pathogen for microbiologically evaluable patients including microbiologically evaluable patients with vancomycin-resistant *Enterococcus faecium* from the extension of this study.

Table 14. Cure Rates at the Test-of-Cure Visit for Intent to Treat, Modified Intent to Treat, and Clinically Evaluable Pediatric Patients for the Overall Population and by Select Baseline Diagnosis

Population	ITT		MITT*		Clinically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)
Any diagnosis	150/186 (81)	69/83 (83)	86/108(80)	44/49 (90)	106/117(91)	49/54 (91)
Complicated skin and skin structure infections	61/72 (85)	31/34 (91)	37/43 (86)	22/23 (96)	46/49 (94)	26/27 (96)

Nosocomial pneumonia	13/18 (72)	11/12 (92)	5/6 (83)	4/4 (100)	7/7 (100)	5/5 (100)
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* MITT = ITT patients with an isolated Gram-positive pathogen at baseline.

Table 15. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Pediatric Patients with Infections due to Gram-positive Pathogens

Pathogen	Microbiologically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)
Vancomycin-resistant <i>Enterococcus faecium</i>	6/8 (75)*	0/0 (-)
<i>Staphylococcus aureus</i>	36/38 (95)	23/24 (96)
Methicillin-resistant <i>S. aureus</i>	16/17 (94)	9/9 (100)
<i>Streptococcus pyogenes</i>	2/2 (100)	1/2 (50)

*Includes data from 7 patients enrolled in the open-label extension of this study.

Pharmacodynamics

In a randomized, positive- and placebo-controlled crossover thorough QT study, 40 healthy subjects were administered a single ZYVOX 600 mg dose via a 1 hour IV infusion, a single ZYVOX 1200 mg dose via a 1 hour IV infusion, placebo, and a single oral dose of positive control. At both the 600 mg and 1200 mg ZYVOX doses, no significant effect on QTc interval was detected at peak plasma concentration or at any other time.

[Pharmacology and toxicology]

Linezolid is a synthetic antibacterial agent of the oxazolidinone class, which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The *in vitro* spectrum of activity of linezolid also includes certain Gram-negative bacteria and anaerobic bacteria. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is essential for bacterial reproduction. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of strains.

In vitro studies have shown that point mutations in the 23S rRNA are associated with linezolid resistance. Reports of vancomycin-resistant *Enterococcus faecium* becoming resistant to linezolid during its clinical use have been published. In one report nosocomial spread of vancomycin- and linezolid-resistant *E. faecium* occurred. There has been a report of *Staphylococcus aureus* (methicillin-resistant) developing resistance to linezolid during its clinical use. The linezolid resistance in these organisms was associated with a point mutation in the 23S rRNA (substitution of thymine for guanine at position 2576) of the organism. Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to linezolid. Also

linezolid resistance in staphylococci mediated by the enzyme methyltransferase has been reported. This resistance is mediated by the *cfr* (chloramphenicol-florfenicol) gene located on a plasmid which is transferable between staphylococci.

Interaction with Other Antimicrobial Drugs

In vitro studies have demonstrated additivity or indifference between linezolid and vancomycin, gentamicin, rifampin, imipenem-cilastatin, aztreonam, ampicillin, or streptomycin.

Linezolid has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecium (vancomycin-resistant strains only)

Staphylococcus aureus (including methicillin-resistant strains)

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for linezolid. However, the safety and effectiveness of linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecalis (including vancomycin-resistant strains)

Enterococcus faecium (vancomycin-susceptible strains)

Staphylococcus epidermidis (including methicillin-resistant strains)

Staphylococcus haemolyticus

Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms

Pasteurella multocida

Toxicology

Mutagenesis

Neither mutagenic nor clastogenic potential was found in a battery of tests including: assays for mutagenicity (Ames bacterial reversion and CHO cell mutation), an *in vitro* unscheduled DNA synthesis (UDS) assay, an *in vitro* chromosome aberration assay in human lymphocytes, and an *in vivo* mouse micronucleus assay.

Impairment of fertility

Linezolid did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ≥ 50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). The reversible fertility effects were mediated through altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. Epithelial cell hypertrophy and hyperplasia in the epididymis was observed in conjunction with decreased fertility. Similar epididymal changes were not seen in dogs.

In sexually mature male rats exposed to drug as juveniles, mildly decreased fertility was observed following treatment with linezolid through most of their period of sexual development (50 mg/kg/day from days 7 to 36 of age, and 100 mg/kg/day from days 37 to 55 of age), with exposures up to 1.7-fold greater than mean AUCs observed in pediatric patients aged 3 months to 11 years. Decreased fertility was not observed with shorter treatment periods, corresponding to exposure *in utero* through the early neonatal period (gestation day 6 through post-natal day 5), neonatal exposure (post-natal days 5 to 21), or to juvenile exposure (post-natal days 22 to 35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats treated from post-natal day 22 to 35.

Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.06-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen.

In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased post-implantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion.

In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternbrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day.

In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.06-fold the estimated human exposure based on AUCs).

When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on post-natal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in pre-implantation loss.

Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk.

Carcinogenesis

Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of linezolid.

Others

Target organs of linezolid toxicity were similar in juvenile and adult rats and dogs. Dose- and time-dependent myelosuppression, as evidenced by bone marrow hypocellularity/decreased hematopoiesis, decreased extramedullary hematopoiesis in spleen and liver, and decreased levels of circulating erythrocytes, leukocytes, and platelets have been seen in animal studies. Lymphoid depletion occurred in thymus, lymph nodes, and spleen. Generally, the lymphoid findings were associated with anorexia, weight loss, and suppression of body weight gain, which may have contributed to the observed effects.

In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed in males dosed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was evident in 2 male rats after 6 months of dosing, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The nerve degeneration observed was microscopically comparable to spontaneous unilateral optic nerve degeneration reported in aging rats and may be an exacerbation of common background change.

These effects were observed at exposure levels that are comparable to those observed in some human subjects. The hematopoietic and lymphoid effects were reversible, although in some studies, reversal was incomplete within the duration of the recovery period.

[Pharmacokinetics]

The mean pharmacokinetic parameters of linezolid in adults after single and multiple oral and intravenous (IV) doses are summarized in Table 16. Plasma concentrations of linezolid at steady-state after oral doses of 600 mg given every 12 hours (q12h) are shown in Figure 1.

Table 16. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	C _{max} µg/mL	C _{min} µg/mL	T _{max} hrs	AUC* µg • h/mL	t _{1/2} hrs	CL mL/min
400 mg tablet single dose **	8.10 (1.83)	---	1.52 (1.01)	55.10 (25.00)	5.20 (1.50)	146 (67)
	11.00 (4.37)	3.08 (2.25)	1.12 (0.47)	73.40 (33.50)	4.69 (1.70)	110 (49)
600 mg tablet single dose	12.70 (3.96)	---	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg IV injection ***	12.90 (1.60)	---	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)
600 mg oral suspension single dose	11.00 (2.76)	---	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)

* AUC for single dose = AUC_{0-∞}; for multiple-dose = AUC_{0-τ}.

** Data dose-normalized from 375 mg.

*** Data dose-normalized from 625 mg, IV dose was given as 0.5-hour infusion.

C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; T_{max} = Time to C_{max};
AUC = Area under concentration-time curve; t_{1/2} = Elimination half-life; CL = Systemic clearance.

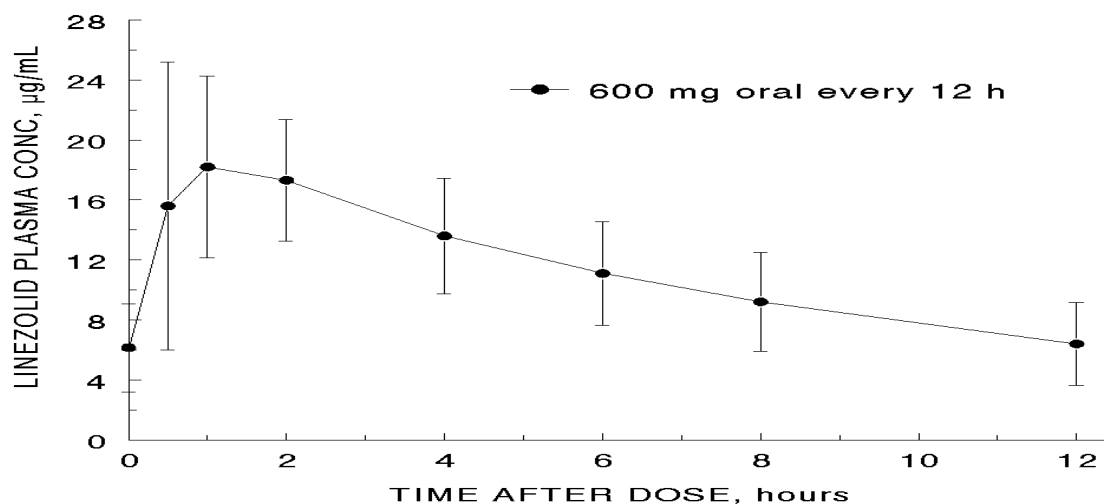


Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-State Following Oral Dosing Every 12 Hours (Mean ± Standard Deviation, n=16).

Absorption: Linezolid is rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute

bioavailability is approximately 100%. Therefore, linezolid may be given orally or intravenously without dose adjustment.

Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as $AUC_{0-\infty}$ values is similar under both conditions.

Distribution: Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well-perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent. The volume of distribution of linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase 1 volunteer studies following multiple dosing of linezolid. The ratio of linezolid in saliva relative to plasma was 1.2 to 1 and for sweat relative to plasma was 0.55 to 1.

Metabolism: Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid metabolite (A), and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a non-enzymatic chemical oxidation mechanism *in vitro*. *In vitro* studies have demonstrated that Linezolid is minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of linezolid is not fully understood.

Excretion: Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as linezolid, 40% as metabolite B, and 10% as metabolite A. The renal clearance of linezolid is low (average 40 mL/min) and suggests net tubular reabsorption. Virtually no linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B, and 3% as metabolite A.

A small degree of non-linearity in clearance was observed with increasing doses of linezolid, which appears to be due to lower renal and non-renal clearance of linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

Special populations

Geriatric: The pharmacokinetics of linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

Pediatric: The pharmacokinetics of linezolid following a single IV dose were investigated in pediatric patients ranging in age from birth through 17 years (including premature and full-term neonates), in healthy adolescent subjects ranging in age from 12 through 17 years, and in pediatric patients ranging in age from 1 week through 12 years. The pharmacokinetic parameters of linezolid are summarized in Table 17 for the pediatric populations studied and healthy adult subjects after administration of single IV doses.

The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age in pediatric patients. However, clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from <1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours (q12h). Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h (see [Dosage and administration]).

Table 17. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

Age Group	C_{max} µg/mL	V_{ss} L/kg	AUC* µg•h/mL	$t_{1/2}$ hrs	CL mL/min/kg
Neonatal Patients					
Pre-term** <1 week (N=9)†	12.7 (30%) [9.6, 22.2]	0.81 (24%) [0.43, 1.05]	108 (47%) [41, 191]	5.6 (46%) [2.4, 9.8]	2.0 (52%) [0.9, 4.0]
Full-term***<1 week (N=10)†	11.5 (24%) [8.0, 18.3]	0.78 (20%) [0.45, 0.96]	55 (47%) [19, 103]	3.0 (55%) [1.3, 6.1]	3.8 (55%) [1.5, 8.8]
Full-term*** ≥1 week to ≤28 days (N=10)†	12.9 (28%) [7.7, 21.6]	0.66 (29%) [0.35, 1.06]	34 (21%) [23, 50]	1.5 (17%) [1.2, 1.9]	5.1 (22%) [3.3, 7.2]
Infant Patients >28 days to <3 Months (N=12)†	11.0 (27%) [7.2, 18.0]	0.79 (26%) [0.42, 1.08]	33 (26%) [17, 48]	1.8 (28%) [1.2, 2.8]	5.4 (32%) [3.5, 9.9]
Pediatric Patients 3 months through 11 years† (N=59)	15.1 (30%) [6.8, 36.7]	0.69 (28%) [0.31, 1.50]	58 (54%) [19, 153]	2.9 (53%) [0.9, 8.0]	3.8 (53%) [1.0, 8.5]

Adolescent Subjects and Patients 12 through 17 years [‡] (N=36)	16.7 (24%) [9.9, 28.9]	0.61 (15%) [0.44, 0.79]	95 (44%) [32, 178]	4.1 (46%) [1.3, 8.1]	2.1 (53%) [0.9, 5.2]
Adult Subjects [§] (N= 29)	12.5 (21%) [8.2, 19.3]	0.65 (16%) [0.45, 0.84]	91 (33%) [53, 155]	4.9 (35%) [1.8, 8.3]	1.7 (34%) [0.9, 3.3]

* AUC = Single dose AUC_{0-∞}

** In this data set, “pre-term” is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a post-natal age between 1 week and 28 days).

*** In this data set, “full-term” is defined as ≥34 weeks gestational age.

† Dose of 10 mg/kg.

‡ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg.

§ Dose normalized to 600 mg.

C_{max} = Maximum plasma concentration; V_{ss} = Volume of distribution, AUC = Area under concentration-time curve;

t_{1/2} = Apparent elimination half-life; CL = Systemic clearance normalized for body weight.

Gender: Females have a slightly lower volume of distribution of linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. After a 600-mg dose, mean oral clearance is approximately 38% lower in females than in males. However, there are no significant gender differences in mean apparent elimination-rate constant or half-life. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

Renal insufficiency: The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal insufficiency; however, the two primary metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction (see Table 18). The clinical significance of accumulation of these two metabolites has not been determined in patients with severe renal insufficiency. Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal insufficiency. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites. Both linezolid and the two metabolites are eliminated by dialysis. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Approximately 30% of a dose was eliminated in a 3-hour dialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after hemodialysis.

Table 18. Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Patients with Varying Degrees of Renal Insufficiency After a Single 600-mg Oral Dose of Linezolid

Parameter	Healthy Subjects CL _{CR} > 8 0 mL/min	Moderate Renal Impairment 30 < CL _{CR} < 80 mL/min	Severe Renal Impairment 10 < CL _{CR} < 30 mL/min	Hemodialysis-Dependent	
				Off Dialysis*	On Dialysis
Linezolid					
AUC _{0-∞} , µg h/mL	110 (22)	128 (53)	127 (66)	141 (45)	83 (23)
t _{1/2} , hours	6.4 (2.2)	6.1 (1.7)	7.1 (3.7)	8.4 (2.7)	7.0 (1.8)
Metabolite A					
AUC ₀₋₄₈ , µg h/mL	7.6 (1.9)	11.7 (4.3)	56.5 (30.6)	185 (124)	68.8 (23.9)
t _{1/2} , hours	6.3 (2.1)	6.6 (2.3)	9.0 (4.6)	NA	NA
Metabolite B					
AUC ₀₋₄₈ , µg h/mL	30.5 (6.2)	51.1 (38.5)	203 (92)	467 (102)	239 (44)
t _{1/2} , hours	6.6 (2.7)	9.9 (7.4)	11.0 (3.9)	NA	NA

* between hemodialysis sessions.

NA = Not applicable.

Hepatic insufficiency: The pharmacokinetics of linezolid are not altered in patients (n=7) with mild-to-moderate hepatic insufficiency (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency has not been evaluated.

[Storage]

Being protected from sunlight and well closed, store at 15°C - 30°C. Avoid frozen.

[Package]

Freeflex packaging system, available in single-use, ready-to-use flexible plastic infusion bags packaging system.

[Shelf-life]

24 months

[Specification number]

Imported Drug Specification JX20180010

[Approval number]

GuoYaoZhunZi HJ20160301

[Drug Marketing Authorization Holder]

Name: Pfizer AS

Registered Address: P.O. Box 3, 1324 Lysaker, Norway

[Manufacturer]

Name: Fresenius Kabi Norge AS

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